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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/902,651	07/12/2001	Hiroyuki Nakanc	77670/495	2816

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 09/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/902,651	NAKANE ET AL.	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 08/898,560.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/14/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 1-32 are pending in the application.

[2] Applicants' amendment to the specification and addition of claims 19-34, filed July 12, 2001, is acknowledged.

[3] The numbering of claims is not in accordance with 37 CFR 1.173, which states "tMisnumbered claims 19-34 been renumbered 17-32.Receipt of an information disclosure statement (IDS), filed May 14, 2002, is acknowledged.

Priority

[5] Applicant's claim to foreign priority under 35 USC § 119(a)-(d) to Japanese patent application 08-213211, filed July 24, 1996, is acknowledged. It is noted that a certified priority document and an English language translation thereof have been filed in application 08/898,560.

Information Disclosure Statement

[6] It is noted that MPEP 1406 directs the examiner to consider all references cited in the original prosecution of the patent. Due to the significant number of references cited by applicants in the original prosecution, the examiner requests that applicants provide a Form PTO-1449 including all references cited in the original prosecution of the patent.

[7] The reference cited in the IDS filed May 14, 2002 has been considered by the examiner. It is noted that this is a foreign language document and applicant has provided what appears to be an English language translation of the cited reference. Applicants are requested to verify that this is an English language translation of the cited reference.

Specification/Informalities

[8] The amendment to the specification, filed July 12, 2001 is objected to as being in an improper format. Applicants are advised that amendments to the specification should meet the requirements of 37 CFR 1.173(b)(1). Amendments should include underlining for newly added matter and bracketing for omitted matter and paragraphs and changes to the specification must be made by submission of the entire text of an added or rewritten paragraph.

[9] It is noted that applicants agree to surrender the original patent upon reissue of the patent (see item 12 of the Declaration filed July 12, 2001). Applicants are reminded that the original patent, or a statement as to loss or inaccessibility of the original patent, must be received before this reissue application can be allowed. See 37 CFR 1.178.

[10] The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: --Mutant Prenyl Diphosphate Synthase--.

[11] Receipt of a substitute sequence listing in computer readable form, a paper copy thereof, and a statement of their sameness, filed January 07, 2002, is acknowledged.

While applicants state, "[t]he Sequence Listing does not go beyond the disclosure in the above-identified application as filed," it is not clear as to whether this statement is meant to be a statement that the paper copy of the sequence listing does not introduce matter into the specification. In order to clarify the record, the examiner requests that applicants state that the paper copy of the sequence listing does not introduce new matter into the specification.

Claim Objections

[12] Claims 1 and 16-32 are objected to as being in an improper format. Applicants are advised that amendments to the specification should meet the requirements of 37 CFR 1.173(b)(2). Applicants are advised that future claim amendments should comply with the requirements of 37 CFR 1.173(b)(2). Applicants are further advised that future amendments to the claims must be based on the original claims.

[13] Claims 1 is objected to because of the following informalities: the term "one amino acid positions" is grammatically incorrect and should be replaced with, for example, "one amino acid position." Appropriate correction is required.

[14] Claims 8, 24, and 25 are objected to in the recitation of "SEQ ID No:1." "SEQ ID No:1" should be replaced with "SEQ ID NO:1" in accordance with 37 CFR 1.821(d). Appropriate correction is required.

[15] Applicant is advised that should claims 8-9 be found allowable, claims 24-25 will be objected to under 37 CFR 1.75 as being substantial duplicates thereof. When two claims in an application are duplicates or else are so close in content that they both

cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claim 8 has been construed as being drawn to the polypeptide of SEQ ID NO:1 having a substitution of at least one of Phe77, Thr78, Val80, His81, and Ile84 or one or more amino acids have been inserted between Ile84 and Met85, wherein the polypeptide synthesizes prenyl diphosphate which is shorter than prenyl diphosphate synthesized by a corresponding wild-type enzyme. Claim 9 has been construed as being drawn to the polypeptide of SEQ ID NO:1 having a substitution of at least one of Phe77 with Tyr, Thr78 with Phe or Ser, Val80 with Ile, His81 with Leu or Ala, and Ile84 with Leu or Pro and Ser have been inserted between Ile84 and Met85, wherein the polypeptide synthesizes prenyl diphosphate which is shorter than prenyl diphosphate synthesized by a corresponding wild-type enzyme. The polypeptides of claims 24-25 are of identical scope to the polypeptides of claims 8-9, respectively, and thus are substantial duplicates. It should be noted that claims 8-9 and 24-25 have been interpreted as described above for examination of the claims for meeting the provisions of 35 U.S.C. 101, 112, first and second paragraphs, 102 and 103. If applicants intended interpretation/scope of claims 8-9 is different from the examiner's as described above, applicants are requested to clarify the record by describing their intended interpretation/scope of the claims and why the scope of claims 8-9 is different from that of claims 24-25.

[16] Claim 16 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n).

[17] Claims 17 is objected to because of the following informalities: the term "located at least one amino acid" is grammatically incorrect and should be replaced with, for example, "located at at least one amino acid." Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[18] Claim(s) 1-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claims 1-32 are confusing in that claims 1 and 17 recite the limitation "wherein said mutant prenyl diphosphate synthase synthesizes prenyl diphosphate which is shorter than prenyl diphosphate synthesized by a corresponding wild-type enzyme," however, in view of the evidence provided in Figure 3, it would appear that the mutant enzymes do not have such ability. The wild-type enzyme of Figure 3 is a geranylgeranyl diphosphate synthase denoted as SacGGPS. Figure 3 shows that wild-type and mutant enzymes all have the ability to synthesize FPP. While it is acknowledged that the mutant enzymes have the ability to produce FPP in greater abundance, there is no

indication that the wild-type enzyme lacks the ability to produce FPP or that the mutant enzymes have the ability to produce a prenyl diphosphate that is shorter than that produced by the wild-type.

[b] Claims 1 (claims 2-16 dependent therefrom) 17 (claims 18-32 dependent therefrom) are unclear in the recitation of "an amino acid between D1 and the amino acid residue at the fifth position upstream of D1." Based on the specification and applicants' own arguments in application 08/898,560, it is unclear as to the recited amino acid. From the specification, it would appear that the recited term would refer to an amino acid that is between *and not including* D1 and the amino acid residue at the fifth position upstream of D1. However, in application 08/898,560, a rejection was made under 35 USC 102(b), wherein the examiner rejected claims asserting that a tyrosine (Y) in the subsequence YSLIHD from *B. stearothermophilus* farnesyl diphospate synthase is an amino acid that is between "an amino acid between D1 and the amino acid residue at the fifth position upstream of D1," which is undisputed by applicants (see pages 6-7 of the Office action mailed May 11, 1998 and pages 4-5 of the amendment filed August 07, 1998 in application 08/898,560. It would appear to the examiner that this tyrosine is not *between I* D1 and the amino acid residue at the fifth position upstream of D1, but instead includes D1 the fifth position upstream of D1. Applicants are requested to clarify the meaning of the phrase "an amino acid between D1 and the amino acid residue at the fifth position upstream of D1." In the interest of advancing prosecution, the examiner has interpreted the phrase as an amino acid between *and not including* D1 and the amino acid residue at the fifth position upstream of D1. Applicants

are advised that an interpretation that includes D1 and the amino acid residue at the fifth position upstream of D1 may necessitate a prior art rejection.

[c] Claims 1 (claims 2-16 dependent therefrom) 17 (claims 18-32 dependent therefrom) are indefinite in the recitation of "region II" as it is unclear as to the amino acid sequence that is considered to be a "region II" of a prenyl diphosphate synthase. It is suggested that applicants clarify the meaning of the claims.

[d] Claim 2 (claim 16 dependent therefrom) and 18 are indefinite in the recitation of "wild type prenyl diphosphate synthase" as it is unclear as to whether the "wild type" enzyme is intended to be the unmodified version of the mutant prenyl diphosphate synthase or is intended to be a non-corresponding wild-type enzyme. It is suggested that applicants clarify the meaning of the claim.

[e] Claims 2 (claim 16 dependent therefrom) and 18 are confusing in that it is unclear as to how a mutant polypeptide can synthesize prenyl diphosphate that is shorter than prenyl diphosphate synthesized by a corresponding wild-type enzyme and simultaneously have the "enzymatic activities" of a wild-type prenyl diphosphate synthase. It is suggested that applicants clarify the meaning of the claims.

[f] Claim 4 (claim 16 dependent therefrom) is unclear in the recitation of "homodimer-type" as it is not clear as to the meaning of a polypeptide that is "of the homodimer-type." Is the term meant to indicate a polypeptide that *is* a homodimer (as in claim 20) or is it meant to encompass some other "homodimer-type" form of a polypeptide? It is suggested that applicants clarify the meaning of the claims.

[g] Claims 5-6 (claim 16 dependent therefrom) and 21-22 are indefinite in the recitation of "derived from" as it is unclear as to whether the term is intended to mean "isolated from" or is intended to mean that the polypeptide is a mutated version of an archaea, *S. acidocaldarius,* etc. polypeptide. It is suggested that applicants clarify the meaning of the claims.

[h] The term "thermostable" in claims 7 (claim 16 dependent therefrom) and 23 is unclear absent a statement defining to what the expression level is being compared. The term "thermostable" is a relative term and the claim should define and clearly state as to what the thermostability of the polypeptide is being compared, *e.g.,* thermostable in comparison to a corresponding wild-type enzyme.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[19] Claim(s) 1-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 1 and 17 recite the limitation, "wherein said mutant prenyl diphosphate synthase synthesizes prenyl diphosphate which is shorter than prenyl diphosphate synthesized by a corresponding wild-type enzyme." Applicants cited support for this recited limitation is at page 10, lines 33-36 of the specification of application 08/898,560 (see page 3, top of Paper No. 13, filed August 07, 1998). However, the examiner can find no support for this limitation at page 10, lines 33-36 of the specification of application 08/898,560 or anywhere else in the specification, claims, and/or drawings as originally filed. Instead, the examiner can find support for "[t]he mutant prenyl diphosphate synthase of the present invention can synthesize a *farnesyl diphosphate* having a shorter chain length than the prenyl diphosphate synthesized by the native prenyl diphosphate synthase" (italics added for emphasis). Applicants are invited to demonstrate support for the recited limitation.

[20] Claim(s) 17-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 17 recites the limitation, "domain having the sequence $D_1D_2X_1(X_2X_3)X_4D_3$... ...and X_2 and X_3 are each optionally independently present." Applicants provide no specifically cited support for this recited limitation. Moreover, the examiner can find no support for this limitation in the specification, claims, and/or

drawings as originally filed. Applicants are invited to demonstrate support for the recited limitation.

[21] Claim(s) 1-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1-10, and 17-26 are drawn to a genus of mutant prenyl diphosphate synthase polypeptides having an aspartic acid-rich domain as set forth in claims 1 and 19 and optionally having the mutations of SEQ ID NO:1 as set forth in claims 8-9 and 24-25, wherein the mutant prenyl diphosphate synthase synthesizes prenyl diphosphate that is shorter than prenyl diphosphate synthesized by a corresponding wild-type enzyme. Claims 11-16 and 27-32 are drawn to nucleic acids, host cells, processes for producing mutant enzymes, and processes for producing prenyl diphosphate.

The Federal Circuit (in *UC California v. Eli Lilly* 43 USPQ2d 1398) has said that a sufficient written description of a genus of DNAs may be achieved by a recitation of a representative number of DNAs defined by nucleotide sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. A representative number of species may be described by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.,* structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient

to show the applicant was in possession of the claimed genus. MPEP § 2163 states that a "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only five representative species of the recited genus of mutant prenyl diphosphate synthases, *i.e.,* Mutant enzyme 1: SEQ ID NO:1 having Thr78 replaced with Phe and His81 replaced with Ala; Mutant enzyme 2: SEQ ID NO:1 having Thr78 replaced with Phe and His81 replaced with Leu; Mutant enzyme 3: SEQ ID NO:1 having Phe77 replaced with Tyr, Thr78 replaced with Phe, and His81 replaced with Leu; Mutant enzyme 4: SEQ ID NO:1 having Phe77 replaced with Tyr, Thr78 replaced with Phe, and His81 replaced with Ala; Mutant enzyme 5: SEQ ID NO:1 having Phe77 replaced with Tyr, Thr78 replaced with Ser, Val80 replaced with Ile, Ile84 replaced with Leu, and an insertion of Pro and Ser between Ile84 and Met85, wherein all mutants have farnesyl diphosphate enzymatic activity. Other than these representative examples, the specification fails to describe any additional representative species of the recited genus of mutant prenyl diphosphate synthases as encompassed by the claims. In this case, the genus encompasses all species having the minimal structural feature of the domains as set forth in claims 1 or 17. While this structural feature is common to all members of the genus, it does not constitute a substantial portion of the genus as the remainder of the structure of polypeptide that synthesizes prenyl diphosphate that is shorter than prenyl diphosphate synthesized by a corresponding wild-type enzyme is completely undefined.

Thus, one of skill in the art must reconstruct the remaining structural features of each member of the genus to achieve a polypeptide that synthesizes prenyl diphosphate that is shorter than prenyl diphosphate synthesized by a corresponding wild-type enzyme. Further, while the specification discloses that the representative mutant prenyl diphosphate synthases exhibit farnesyl diphosphate synthase activity (see column 14, bottom), the members of the claimed genus can broadly possess activity that synthesizes prenyl diphosphate that is shorter than prenyl diphosphate synthesized by a corresponding wild-type enzyme. The five representative species of the genus of claimed mutant prenyl diphosphate synthases fail to describe all members of the genus, which encompasses *widely* variant species with respect to structure, *i.e.,* amino acid sequence and function. Given the lack of description of a representative number of species and lack of recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[22] Claims 1-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polypeptide of SEQ ID NO:1 having a substitution of at least one of Phe77, Thr78, Val80, His81, and Ile84 with another amino acid or one or more amino acids have been inserted between Ile84 and Met85, wherein the polypeptide has farnesyl diphosphate synthase activity, nucleic acids encoding therefor, a host cell transformed with a recombinant vector encoding said polypeptide, a

process for producing said polypeptide, and a process for producing farnesyl diphosphate, does not reasonably provide enablement for *all* mutant prenyl diphosphate synthases, nucleic acids encoding therefor, *all* host organisms, processes for producing said polypeptide, and a process for making *all* prenyl diphosphates as broadly encompassed by the claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

- The claims are overly broad in scope: Regarding claims drawn to polypeptides, the claims are so broad as to encompass a vast number of mutant prenyl diphosphate synthase polypeptides having the minimal structural feature recited in claims 1 and 17 and having the activity of synthesizing prenyl diphosphate which is shorter than prenyl diphosphate synthesized by a corresponding wild-type enzyme. Regarding claims drawn to host organisms, this term broadly encompasses any host including transgenic

plants and mammals. Regarding claims drawn to a process for making prenyl diphosphates, it is noted that the claims broadly encompass methods for making any prenyl diphosphate. The broad scope of claimed polypeptides and host organisms is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides and host organisms broadly encompassed by the claims. In this case the disclosure is limited to the polypeptide of SEQ ID NO:1 having a substitution of at least one of Phe77, Thr78, Val80, His81, and Ile84 with another amino acid or one or more amino acids have been inserted between Ile84 and Met85, wherein the polypeptide has farnesyl diphosphate enzyme activity, a host cell transformed with a recombinant vector encoding said polypeptide, and a method of making farnesyl diphosphate using said polypeptide.

- The lack of guidance and working examples: Regarding claims drawn to polypeptides, the specification provides only five working examples of the scope of claimed polypeptides, *i.e.,* Mutant enzyme 1: SEQ ID NO:1 having Thr78 replaced with Phe and His81 replaced with Ala; Mutant enzyme 2: SEQ ID NO:1 having Thr78 replaced with Phe and His81 replaced with Leu; Mutant enzyme 3: SEQ ID NO:1 having Phe77 replaced with Tyr, Thr78 replaced with Phe, and His81 replaced with Leu; Mutant enzyme 4: SEQ ID NO:1 having Phe77 replaced with Tyr, Thr78 replaced with Phe, and His81 replaced with Ala; Mutant enzyme 5: SEQ ID NO:1 having Phe77 replaced with Tyr, Thr78 replaced with Ser, Val80 replaced with Ile, Ile84 replaced with Leu, and an insertion of Pro and Ser between Ile84 and Met85, wherein all mutants have farnesyl diphosphate enzyme activity. These working examples fail to provide the necessary

guidance for making the entire scope of claimed polypeptides. The specification fails to provide guidance regarding those amino acids of SEQ ID NO:1 that may be altered by substitution, insertion, addition and/or deletion with an expectation of maintaining the desired biological activity. Further, applicants acknowledge that the product of the mutant enzymes is farnesyl diphosphate (see pp. 4-5 of Paper No.13 of Application 08/898,560, filed August 07, 1998) and the specification teaches that the reaction product of the mutant prenyl diphosphate synthases was farnesyl diphosphate (column 14, bottom). The specification fails to provide guidance for altering the sequence of SEQ ID NO:1 such that the altered polypeptide will have the ability to synthesize any prenyl diphosphate that is shorter than prenyl diphosphate synthesized by a corresponding wild-type enzyme. Regarding the claimed host organisms, the specification provides a number of working examples of host organisms (column 7), however, these hosts are *cells* and the specification fails to provide guidance for transforming any host organism including any plant or mammal. Regarding claims drawn to processes of making a prenyl phosphate, the specification fails to teach how to make any prenyl phosphate(s) using the disclosed mutants or mutants as broadly encompassed by the claims.

- The high level of unpredictability in the art: Regarding polypeptide claims, the amino acid sequence of a polypeptide determines its structural and functional properties. Predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (*i.e.,* expectedly intolerant to modification), and

detailed knowledge of the ways in which the protein's structure relates to its function. The positions within a protein's sequence where modifications can be made with a reasonable expectation of success in obtaining an encoded polypeptide having the desired activity/utility are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, *e.g.,* multiple substitutions. In this case, the necessary guidance has not been provided in the specification as explained in detail above. Thus, a skilled artisan would recognize the high degree of unpredictability that the entire scope of polynucleotides would encode a polypeptide having the desired activity. Regarding host organisms, the ability to transform any host including plants and mammals with a polynucleotide with an expectation of expressing the encoded protein is highly unpredictable. Regarding claims drawn to processes of making a prenyl phosphate, one of skill in the art would recognize the high level of unpredictability in making any prenyl phosphate using an enzyme that has farnesyl diphosphate activity.

- The state of the prior art supports the high level of unpredictability: The state of the art provides evidence for the high degree of unpredictability in altering a polypeptide sequence with an expectation that the altered polypeptide will have the desired activity/utility. For example, Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York, 1991) teach "[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising

results of such experiments reveal how little we know about the rules of protein stability... ...they also serve to emphasize how difficult it is to design *de novo* stable proteins with specific functions" (page 247). Witkowski et al. (*Biochemistry* 38:11643-11650) exemplify the teachings of Branden et al. by disclosing that a single amino acid substitution results in conversion of the parent polypeptide's activity from a beta-ketoacyl synthase to a malonyl decarboxylase (see e.g., Table 1, page 11647). The reference of Ohnuma et al. (*J. Biol Chem* 271:10087-10095; cited in the IDS filed October 21, 1997, Paper No. 8, of application 08/898,560). Applicants do not dispute that Ohnuma et al. teach a *B. stearothermophilus* geranylgeranyl diphosphate synthase having a mutation at the fifth amino acid (Tyr81) upstream of Asp86 of the acid-rich domain and acknowledge the mutant of Ohnuma et al. catalyzes the biosynthesis of a product that is *longer* than the substrate (see page 4 of Paper No. 13, filed August 07, 1998 of application 08/898,560). Thus, the prior art acknowledges the unpredictability of altering a protein-encoding sequence with an expectation of obtaining a protein having a desired function and discloses that even a single substitution in a polypeptide's amino acid sequence may completely alter the function of a polypeptide.

- The amount of experimentation required is undue: While methods of generating variants of a given polypeptide are known in the art, *e.g.,* mutagenesis, it is not routine in the art to screen for *all* polypeptides having a substantial number of substitutions or modifications as encompassed by the instant claims for those that have the ability to synthesize any prenyl diphosphate that is shorter than prenyl diphosphate synthesized by a corresponding wild-type enzyme. Also, it is not routine to attempt to transform all

host organisms including any plant or human to screen those that can successfully be transformed and express the encoded polynucleotide. Further, it is not routine to screen all mutant enzymes for those that have the ability to produce any prenyl phosphate as encompassed by the claims.

Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation that is required, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Conclusion

[23] Status of the claims:

- Claims 1-32 are pending.
- Claims 1-32 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Friday from 6:30 am to 4:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The FAX number for submission of official papers to Group 1600 is (703) 872-9306. Draft or informal FAX communications should be directed to (571) 273-0942. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman

David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1652
09-15-04